PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of

Mohamed CHOKRI et al.

Serial No. 09/304,564

Filed May 4, 1999

Examiner A. Holleran

MACROPHAGES, PROCESS FOR PREPARING THE SAME AND THEIR USE AS ACTIVE SUBSTANCES OF PHARMACEUTICAL COMPOSITIONS

APPEAL BRIEF

#15

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1. **Real Party in Interest**

The real party in interest in this appeal is the assignee, IDM Immuno-Designed Molecules of Paris, France.

2. **Related Appeals and Interferences**

Appellant is unaware of any other appeals or interferences that will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

3. **Status of Claims**

Claims 1 and 2 have been canceled. Claims 3-5 are pending in this application, and the present appeal is taken from the final rejection of all of Claims 3-5.

4. **Status of Amendments**

No amendment was filed subsequent to final rejection of the claims on appeal.

5. **Summary**

The invention is a method for treating cancer, which comprises administering both (1) activated macrophages as described for example at page 3, lines 1-14 of the specification, and (2) bispecific antibodies as described for example at page 10, lines 1-11 of the present specification.

In particular, the macrophages administered in the claimed method are characterized by having at least one of the following properties:

(1) their cytotoxic activity without IFN-γ is increased by about 20 to 30% with respect to standard macrophages; (2) their cytotoxic activity with IFN-γ is increased by about 20 to about 40% with respect to standard macrophages; and (3) deactivation of the cytotoxic activity following activation of IFN-γ is such that sixty hours after activation with IFN-γ, the residual cytotoxic activity is at least 30% of the maximum cytotoxic activity presented by the macrophages due to IFN-γ activation, with this cytotoxic activity being measured as a percentage of the inhibition of 3-H thymidine incorporation by target tumoral cells, particularly U 937 cells. (See claim 3 on

appeal.)

The bispecific antibodies administered in the claimed method are those which recognize both a) an antigen of these macrophages, and b) an antigen of a tumoral cell to be targeted by these macrophages. (See claim 3 on appeal.)

The macrophages according to the invention are produced by *ex vivo* differentiation of blood monocytes, under culture conditions conferring the improved properties recited in the present claims relative to standard macrophages.

It bears noting that the patentability of the claimed macrophages *per se*, as well as the patentability of methods for treating cancer using such macrophages, is already established. Specifically, claim 1 of U.S. Patent No. 5,662,899 claims macrophages having the same properties as those of the claims on appeal, and claim 2 of U.S. Patent No. 6,001,351 claims a method for treating cancer comprising administering such macrophages, with the further proviso that the macrophages contain exogenous nucleic acids and/or drugs. Both of these patents issued on ancestor applications of the present application. Copies of U.S. Patents Nos. 5,662,8999 and 6,001,351 are attached for ease of reference.

6. **Issues**

The issues on appeal are as follows:

(1) Whether Claims 3-5 are suitably definite, within the meaning of the second paragraph of 35 USC §112;

(2) Whether Claims 3-5 are anticipated under 35 USC §102(b) by Chokri et al. (Chokri, M et al., Res. Immunol., 143: 95-99, 1992); and

(3) Whether Claims 3-5 are anticipated under 35 USC §102(e) by Fanger et al., U.S. Patent No. 5,635,600 or anticipated under 35 USC §102(b) as anticipated by WO 91/05871 (Medarex, Inc. published May 2, 1991).

7. Grouping of Claims

The claims are not grouped separately for purposes of the present appeal, with claim 3 being representative.

8. Argument

(a) The Claims are Suitably Definite

The final rejection does not contend that the scope of any of the claims on appeal is in any way unclear. Instead, the final rejection contends that the claims "are broader in scope than what applicant's [sic] appear to regard as their invention." The Examiner cites Paper No. 7 filed January 4, 2001 in support of that contention.

The indefiniteness rejection is therefore fatally flawed for multiple reasons. First, the claims presumptively set

forth what the Applicant regards as his invention. The second paragraph of 35 USC §112 is therefore satisfied when the claims have an understandable scope, which the Examiner does not dispute.

Second, nothing in Paper No. 7 filed January 4, 2001 would suggest that Applicants regard their invention as being narrower than the scope of claim 3 on appeal. The present invention is there clearly distinguished from the prior art based on the intrinsic properties of the claimed macrophages. That those properties can be imparted by a range of processing conditions does not require the processing conditions to be recited in the claims, much less does it evidence any belief by the Applicants that their invention is limited to any particular processing conditions; indeed the language of the claims themselves is conclusively contrary to any such assumption.

It is therefore believed to be apparent that the indefiniteness rejection must be reversed.

(b) Claims 3-5 are not anticipated by Chokri et al.

The final rejection contends that the macrophages of Chokri et al showed an increase in cytotoxic activity within the range of this claimed invention, when they were administered in conjunction with bispecific antibodies. However, the claims on appeal require that the macrophages themselves exhibit the claimed properties. Therefore, even if the Examiner's contentions with respect to Chokri et al. were accurate, they

would not support a rejection of any of the claims on appeal.

The impropriety of the anticipation rejection based on Chokri et al. is underscored by the fact that Chokri et al. is a cited reference in both of U.S. Patents Nos. 5,662,8999 and 6,001,351 (see attached copies). Thus, the position of the present Examiner that Chokri et al. teaches the claimed macrophages, in addition to being mistaken on the merits, is also flatly inconsistent with the allowance of claim 1 in U.S. Patent No. 5,662,899, which claims macrophages having the identical properties.

The implicit contention of the present Examiner, in rejecting the claims on appeal based on the previously-considered Chokri et al. article, is therefore that the Examiner who acted on the attached U.S. Patents Nos. 5,662,8999 and 6,001,351 did not do her job correctly, and in fact that at least claims 1 of U.S. Patent No. 5,662,899 is invalid based on prior art of record in that patent. Again, in addition to the substantive impropriety of that position, as discussed above, the present Examiner's position would seem to run afoul of the restrictions imposed by MPEP §1701.

It is therefore believed also to be apparent that the rejection based on Chokri et al is improper and must be reversed.

(c) Claims 3-5 are not anticipated by Fanger or Medaraex

The rejections based on Fanger and Medaraex are based on wholly unsupported contentions by the Examiner that the

macrophages mentioned in those references are the same as those required by the claims on appeal. Again, we point out that the position of the present Examiner would seriously disparage the validity of at least claim 1 of the attached U.S. Patent No. 5,662,899, in violation of MPEP §1701, given that claim 1 of the `899 patent specifically claims macrophages having the same intrinsic properties called for in the claims on appeal.

In fact, however, the macrophages used in the claimed methods are distinctly different than those of the Fanger and Medarex references. The Examiner tacitly acknowledges the shortcomings of these references relative to the claims on appeal, by failing to identify where, in either reference, any of the claimed macrophage properties are disclosed.

Instead, it appears that the entire basis for the Examiner's reliance on these references relative to the claimed macrophages is her allegation, at pp. 4-5 of Paper No. 8, that "[t]he macrophages [of the applied references] may be treated with interferon-gamma." Using only that slender and insufficient reed, the Examiner proceeds to assume that the claimed macrophages and those of the references are "the same," and seeks to impose on Applicants an entirely inappropriate burden of disproving these unwarranted assumptions.

However, the present specification itself teaches, and the claims on appeal require, that the recited macrophages display markedly superior cytotoxic activity relative to standard

macrophages, whether they are activated with or without IFN-γ. Therefore, by definition, mere treatment with interferon gamma is insufficient to produce macrophages as required by the present claims.

It further bears noting that Fanger et al does not teach properties of macrophages by themselves, but rather only in conjunction with bispecific antibodies. Thus, the reference does not teach increasing the macrophage's cytotoxicity without the bispecific antibody coating. Macrophages that are, by themselves, 20 to 30% more cytotoxic than standard macrophages are nowhere taught or suggested by Fanger et al.

Medaraex describes cultivating monocytes in a culture medium in order to differentiate the monocytes into macrophages. However, nothing in this reference teaches producing macrophages in such as way as to increase the cytotoxicity of these macrophages by 20 to 30% over standard macrophages.

Further evidence that the Medarex macrophages do not respond to the requirements of claim 3 on appeal is found in part (a) of claim 18 of Medarex, which requires "an effector cell expressing high affinity Fc-γ receptor." An effector cell (i.e., macrophage), expressing Fc-γ receptors indicates the effector cell is cytotoxic. It is conventional for a macrophage to express Fc-γ receptors, but this applied reference does not teach or suggest macrophages with an increase in cytotoxicity compared to standard macrophages (which may be indicated by an increased

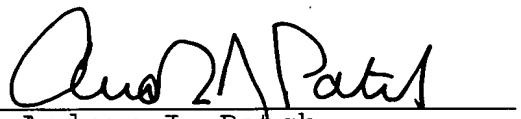
expression of Fc-γ receptors). It merely describes an effector cell with cytotoxic activity as a potential host to bispecific antibodies.

Conclusion

From the above discussion, it is believed to be apparent that the final rejection of claims 3-5 cannot properly be affirmed as to any of the grounds of rejection on appeal, but instead must be reversed. Such action is accordingly respectfully requested.

Respectfully submitted,

YOUNG & THOMPSON

By 

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9. Appendix

The claims on appeal:

3. A method for treating cancer, comprising administering to a patient in need of said treatment

(i) macrophages having at least one of the following properties:

- their cytotoxic activity without IFN-γ is increased by about 20 to 30% with respect to standard macrophages;

- their cytotoxic activity with IFN-γ is increased by about 20 to about 40% with respect to standard macrophages;

- deactivation of the cytotoxic activity following activation of IFN-γ is such that sixty hours after activation with IFN-γ, the residual cytotoxic activity is at least 30% of the maximum cytotoxic activity presented by the macrophages due to IFN-γ activation, with said cytotoxic activity being measured as a percentage of the inhibition of 3-H thymidine incorporation by target tumoral cells, particularly U 937 cells; and

(ii) bispecific antibodies which recognize both a) an antigen of said macrophages, and b) an antigen of a tumoral cell to be targeted by said macrophages.

4. The method according to claim 3, wherein the macrophages are injected at the same time as the bispecific antibodies.

5. The method according to claim 3, wherein the bispecific antibodies are preincubated with macrophages before injection.